

REMARKS

I. Status of the Claims

Claims 3-8, 12-16 and 19 are currently pending. Claims 5-7 and 12 are cancelled herein without prejudice. New claims 20-22 are added.

The withdrawal of the previous grounds of rejection under 35 USC 112 second paragraph, 35 USC 102(b) based on each of Birr and Merrifield as evidenced by Finger is noted with appreciation.

The withdrawal of claim 15 from consideration is respectfully traversed, as discussed in greater detail below.

Submitted herewith in support of this application is the Declaration of Luciano Forni under 37 CR 1.132. Mr. Forni is one of the named inventors of this application, has over thirty years of experience in the field of peptide synthesis, and is of at least ordinary skill in the art in the field of solid phase peptide synthesis (Decl. ¶¶ 2, 3).

II. Summary of Amendments

The present invention relates to a method of solid phase peptide synthesis (SPPS). As is known in the art of SPPS, peptides are synthesized by attaching a protected amino acid or peptide to a resin solid support, deprotecting the amino acid or peptide, coupling a protected amino acid to the deprotected site, then continuing the cycles of deprotection and coupling to build up a peptide having a desired amino acid sequence. (Decl. ¶ 4) Thorough washings are performed after each deprotection step and after each coupling step. (Decl. ¶¶ 5,6)

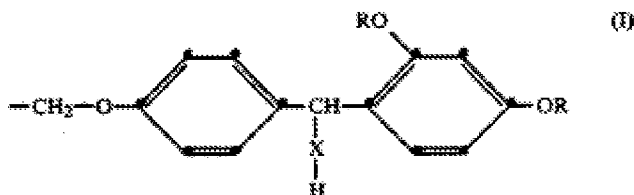
The present invention relates to the discovery that the use of certain salts during various steps in the SPPS process can greatly improve the efficacy of the wash steps, such that fewer wash cycles are needed at each wash step. (Decl. ¶¶ 7-10) The use of such salts in the wash steps is particularly advantageous because the presence of such salts will not interfere with either the deprotection reaction or the coupling reaction. (Decl. ¶¶ 11-12) The claims as originally filed recited the use of such salts in any of the various SPPS steps. In this amendment claims reciting the use of such salts in the coupling steps and deprotection steps are cancelled without prejudice, the applicant expressly reserving the right to pursue the subject matter of those claims in one or more continuing or divisional applications. The remaining claims as presented herein are

limited to those embodiments of the invention in which the recited salt is used in the wash step after the deprotection step, or in the wash step after the coupling step, or in both wash steps.

III. Response to Claim Rejection, §103(a) – Rink, Mihala, Merrifield, and Finger

The rejection of claims 3-8, 12-14, 16 and 19 as obvious under this combination of references is respectfully traversed. Without acquiescing in this ground of rejection, claims 5-7 and 12 are cancelled herein, such that this ground of rejection is moot as to those claims.

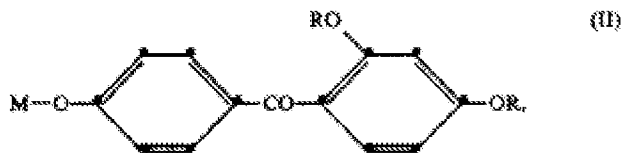
Rink (U.S. 5,004,781) discloses a resin suitable for use in a Merrifield solid phase peptide synthesis, a method for making the resin, and a method of using the resin in solid phase peptide synthesis. The resin of Rink is characterized (col. 1, lines 16-28) in that it has been substituted at benzene rings of its skeletal structure by groups of the formula



in which X represents -O- or -NH- and R represents $\text{C}_1\text{-C}_4$ alkyl.

The method of making the resin is discussed at col. 3, line 6 – col. 5, line 25. In the method of making the resin, a suitable polystyrene is reacted, in succession,

(a) with a compound of formula



in which M is an alkali metal and R has the meaning given above,

(b) with a reducing agent and, if X represents -NH- ,

(c) with a reagent that introduces the amino group.

(Rink, col. 3, lines 36-53) In process step (b) of Rink, the oxo group of formula II is converted to a hydroxyl group (col. 4, lines 10-13). If “X” in formula (I) is to be an -NH- , then the hydroxyl group is converted to an amino group to convert the “hydroxyl resin” to the “amino

resin” (col. 4, lines 32-35). The source of the amino groups can be ammonia gas (col. 4, lines 35-42) or carbamates (col. 4, lines 43-47). “In this manner a synthetic resin of the above-defined structure is obtained that carries instead of the –X-H group a –NH-W group in which W represents an amino-protecting group ...” (col. 5, lines 2-5)

To free the “amino resin” to provide a binding site for subsequent use in peptide synthesis, the amino-protecting group W is removed with a base such as a tertiary or secondary amine (col. 5, lines 7-12), or with “...an alkali metal hydroxide, for example sodium hydroxide, or an ammonium hydroxide, for example benzyltrimethylammonium hydroxide...” (col. 5, lines 19-22). It may be seen that this portion of Rink relates to a method of making a support resin, **not** to a procedure for conducting a Merrifield solid-state peptide synthesis. (Decl. ¶ 14a)

In the previous response, it was pointed out that Rink teaches the use of benzyltrimethylammonium hydroxide only during the step of deprotecting the resin which serves as the solid phase during the peptide synthesis, and not during the actual synthesis of the peptide. (See also, Decl. ¶14b)

As the Action correctly points out, Rink does not teach the use of benzyltrimethylammonium hydroxide at any and all of the process steps, nor does Rink teach its use in any of the examples (Decl. ¶14c). The Action also does not suggest that Rink uses such salts in either of the wash steps, as recited in the present claims.

Mihala teaches a solid phase peptide fragment condensation protocol in which the coupling step (step c of representative claim 3 herein) is conducted in a 3:1 chloroform-phenol solvent system with a combination of 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HODhbt) and its tetrabutylammonium (TBA) salt as additive. (Abstract) Without agreeing that Mihala suggests the use of the claimed salts in any step of the SPPS method of the recited claims, it is respectfully pointed out that Mihala does not teach or suggest the use of such salts in either of the wash steps of the method. Mihala only teaches the use of the particular ammonium salt as a coupling additive (Decl. ¶13a).

With regard to Merrifield, the Action states at page 6, lines 1-2, “Importantly Merrifield teach that the presence of triton B enabled a particular reaction to occur (abstract).” Thus, Merrifield in combination with Finger teaches the use of benzyltrimethylammonium hydroxide in the coupling step, which is called “acylation” by Merrifield (Decl. ¶13b). The salt is used to improve a reaction, not in a wash step as recited in the present claims.

With regard to the comments on page 8 of the Action, Applicants acknowledge that the solid phase peptide synthesis technique is known in the art. What is new and non-obvious in the claims as presented herein is the use of the recited salts in the wash steps. By comparison, the references teach one skilled in the art that the salts are used to enhance reactions, either during SPPS or before SPPS. (Decl. ¶¶16, 17) The references, taken either alone or in combination, do not teach or suggest to one skilled in the art that such salts should be used in either of the wash steps, or that the use of such salts in either of the wash steps advantageously will reduce the number of wash cycles within each wash step. (Decl. ¶¶18, 19)

Therefore, in view of the foregoing and in light of the clarifying amendments to the claims presented herein, Applicants believe that the present claims are not obvious over the cited art, such that this ground of rejection has been overcome.

IV. Rejoinder of Claim 15

In the Office Action of July 24, 2008, the Office required elections of species with respect to the salt and the alpha amino protecting group. The action stated, “Upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of the allowed generic claim as provided by 37 CFR 1.141.” In the present case, all of the independent claims have been shown to be allowable over the cited art of record. Previously withdrawn claim 15, which depends from allowable claim 3 and includes all the limitations thereof, is now entitled to consideration, as stated in the original Action. It is respectfully requested that claim 15 be rejoined in the case.

Conclusion

Applicants submit that the rejections proffered by the Office have been overcome, and that the Application is now in condition for allowance. The Applicants invite the Examiner to contact the undersigned as indicated below if the Examiner believes that this would expedite prosecution of this application.

Respectfully submitted,

Date: November 24, 2010

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